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Factors contributing to the failure of Humidified High-Flow Nasal Cannulae

Sophia Teoh[1], Elizabeth Clyde[1], Theodore Dassios[1,2], Anne Greenough[2,,3,4]

[1]Neonatal Intensive Care Centre, King's College Hospital NHS Foundation Trust, London, UK; [2]Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, UK; [3]MRC & Asthma UK Centre for Allergic Mechanisms in Asthma; [4]NIHR Biomedical Research Centre based at Guy's & St Thomas' Hospital and King's College London, UK

Short title: Prediction of HHFNC failure

Corresponding author: Professor Anne Greenough, Neonatal Intensive Care Unit, 4th Floor Golden Jubilee Wing, King's College Hospital, Denmark Hill, London, SE5 9RS, UK. Tel: 0203 299 3037; fax: 0203 299 8284 Email: anne.greenough@kcl.ac.uk

The use of humidified high-flow nasal cannulae (HHFNC) as an alternative mode of non-invasive ventilation (NIV) in neonates has become widespread. A survey of UK neonatal units showed the proportion using HHFNC had increased from 56% in 2012 to 87% in 2015 (1). A recently reported Cochrane Review (2) comparing the use of HHFNC against other NIV modes of ventilation immediately after birth or following extubation showed no significant difference in the rates of bronchopulmonary dysplasia (BPD) or death and no significant difference in the rates of treatment failure/reintubation. Benefits cited include a significantly reduced risk of nasal trauma as compared to continuous positive airway pressure (CPAP). Furthermore, both medical staff and parents (3) were found to prefer HHFNC to CPAP. Identification of infants in whom use of HHFNC as either a primary or step-down mode of respiratory support may be inappropriate might further reduce the failure rate of HHFNC.

We carried out a retrospective analysis of all infants treated with HHFNC admitted to the neonatal unit of King's College Hospital NHS Foundation Trust (London, UK) between 01/01/2015 and 31/12/2016. Our aim was to identify the clinical and demographic characteristics that might contribute to failure of support by HHFNC. Failure was defined as the need to switch to CPAP or intubation and mechanical ventilation (MV) for recurrent episodes of apnoea, development of a respiratory acidosis ($pH<7.25$ and $pCO_2>8$ kPa) or an inspired oxygen concentration (FiO_2) requirement > 0.6. Success was defined as weaning off all respiratory support or weaning to supplemental oxygen delivered by low-flow nasal cannulae. In infants who had had multiple episodes of support using HHFNC, only the first episode was reviewed. The episode of HHFNC was defined as primary if HHFNC was the primary method of respiratory support used or a step-down episode if it was following from CPAP or MV.

Two hundred and twenty-six infants were identified from whom 134 complete records were available for use. Out of the 134, 32 infants failed HHFNC (Table 1). Infants who failed HHFNC had a lower mean birth weight (p=0.035), higher mean FiO_2 at time of commencing HHFNC (p=0.004) and a higher incidence of positive blood culture up to the time of starting HHFNC (p=0.001). They were also found to have a higher maximum flow rate at the time of starting HHFNC (p=0.004).

Multivariate regression analysis of birth weight, positive blood cultures and FiO_2 using failure of HHFNC as the outcome showed that the mean FiO_2 at the time of starting HHFNC was independently significantly higher in the infants who failed ($p<0.05$) but neither birth weight nor a positive blood culture were significantly different between the failure and success groups. A FiO2 > 28% predicted failure of HHFNC with a sensitivity of 73% and specificity of 61%.

The mean gestational age was higher in the 32 infants who had HHFNC as a primary mode [32 (range 26-40) weeks] than those who had HHFNC as a step down from CPAP or MV [30 (23-41) weeks, p=0.016].The mean birth weight was also higher in infants who had HHFNC as a primary mode [1,805 (range 880 – 4,695) gms] than those who had HHFNC as a step down from CPAP or MV [1,470 (range 510 – 4,400) gms, p=0.04]. The mean corrected gestational age at starting HHFNC was not significantly different between the two groups [33 (range 27 – 44) weeks] versus [33 (range 25 – 48) weeks, p=0.386]. The mean FiO_2 at starting HHFNC was not significantly different between the two groups (0.27 (range 0.21 – 0.45) versus (0.29 (range 25 – 48) weeks, p=0.532).

Our data suggest that failure of HHFNC therapy is more common in neonates with a higher FiO_2 at the time of starting HHFNC. Arguably, a higher oxygen requirement reflects higher underlying lung disease severity as ventilation to perfusion mismatch and the degree of the intrapulmonary right to left shunting correlate with the oxygen requirement (4). The importance of this study is that we report that a higher FiO_2 on starting HHFNC is associated with failure of HHFNC. Manley et al undertook a secondary analysis of a randomized trial comparing HHFNC and CPAP and reached similar conclusions (5). They, however, only used HHFNC as a primary mode of support at birth. In our study, we also assessed infants in whom HHFNC was used as a stepdown mode of support. We should acknowledge limitations of our study which were that records of only 59% of the eligible infants were available and it was a retrospective analysis of non-randomised data. Nevertheless, our results highlight a subgroup of infants who might be unlikely to benefit from HHFNC and may inform entry criteria into randomized trials.

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Table 1: Success versus failure on HHFNC post-extubation (for continuous data sets, results expressed as mean (range); for discrete data sets, NS = not significant).

	Succeeded on HHFNC	Failed on HHFNC	P Value
N	102	32	
Gestational age (GA) (weeks)	30.6 (23 - 41)	29.8 (24 - 39)	0.244
Gender	Female = 39 Male = 63	Female = 12 Male = 20	NS
Antenatal steroids received	None = 21 Incomplete = 63 Complete = 18	None = 8 Incomplete = 21 Complete = 3	NS
Surfactant received	Yes = 41 No = 61	Yes = 10 No = 22	NS
IUGR	Yes = 15 No = 87	Yes = 9 No = 23	NS
Congenital anomalies	Yes = 15 No = 87	Yes = 7 No = 25	NS
Birth weight (g)	1603 (600 - 4694)	1376 (512 - 3146)	0.035
Corrected GA (CGA) at starting HHFNC (weeks)	32.7 (27 - 48)	32.6 (25 - 39)	0.852
HHFNC as primary mode	26	6	0.598
HHFNC as step-down from CPAP/MV	75	27	0.598
Weight at starting HHFNC (g)	1806 (760 - 4990)	1631 (668 - 3480)	0.137
CPAP pressure (cmH_2O) when switched to HHFNC	5.6 (4 - 8)	5.7 (4 - 7)	0.660

FiO_2 at starting HHFNC	0.28 (0.21 - 0.60)	0.34 (0.21 - 0.59)	0.004
CRP at starting HHFNC	8.8 (0 - 109)	6.7 (0 - 48)	0.875
Flow rate (L/min) started on HHFNC	6.03 (3 - 8)	6.30 (4 - 8)	0.195
Maximum flow rate (L/min)	6.18 (3 - 8)	6.83 (5 - 8)	0.004
Duration of HHFNC (days)	10.9 (0 - 89)	9.7 (1 - 38)	0.739
FiO_2 at time failing HHFNC	N/A	0.44 (0.21 - 1.00)	N/A
Patent ductus arteriosus (PDA) at time of starting HHFNC	Yes = 5 No = 97	Yes = 4 No = 28	NS
Caffeinated at time of starting HHFNC	Yes = 66 No = 36	Yes = 20 No = 12	NS
Blood culture at time of starting HHFNC	Positive = 2 Negative = 70 No culture = 30	Positive = 3 Negative = 11 No culture = 18	0.001